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(54) Title: OPHTHALMIC COMPOSITIONS INCLUDING PEPTIDES AND PEPTIDE DERIVATIVES AND METHODS FOR USING SAME (57) Abstract Ophthalmic compositions and methods for preserving and using such compositions are disclosed. In one embodiment, such compositions include a liquid medium, a first antimicrobial component selected from antimicrobial peptides and mixtures thereof, and a second antimicrobial component, other than the first antimicrobial component, which is preferably substantially non-oxidative. Compositions which include a liquid medium and antimicrobial peptide nanotubes effective to disinfect a contact lens present in the liquid medium containing the nanotubes are also disclosed. Preserved compositions useful for caring for contact lenses are included within the scope of the present invention.		

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**OPHTHALMIC COMPOSITIONS INCLUDING PEPTIDES
AND PEPTIDE DERIVATIVES AND METHODS FOR USING SAME**

Background of the Invention

This invention relates to ophthalmic compositions and methods for preserving and using such compositions. More particularly, the present invention relates to ophthalmic compositions, for example, useful in caring for contact lenses, which include one or more peptides and/or peptide derivatives as antimicrobial agents, and to methods for using such compositions, for example, to care for contact lenses.

Various compositions, such as solutions, are used in association with contact lenses to ensure that the lenses may be safely, comfortably and conveniently worn. Contact lens care compositions, for example, disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions and the like, often utilize at least one disinfectant or preservative, depending on the type of composition, for disinfecting contact lenses after wear or for preserving the lens care composition itself.

A contact lens disinfecting composition generally has sufficient antimicrobial activity so that when the composition is contacted with a contact lens to be disinfected, microorganisms associated with the lens are killed or otherwise removed and the contact lens is effectively disinfected within a reasonable time, for example, in the range of about 0.1 hour to about 12 hours. A contact lens disinfecting composition may be termed a microbicidal composition. In contrast, a preserved contact lens care composition has sufficient antimicrobial activity, often less of such activity than is present in a contact lens disinfecting composition, so that when the composition is contacted with a contact lens substantially no increase in the microorganism population on the lens or in the composition is obtained. A preserved contact lens

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care composition may be termed a microbiostatic composition. Contact lens care compositions are often preserved to prevent any substantial increase in, or to gradually decrease, the population of contaminating microorganisms in the compositions and, thereby, to extend their shelf life. Some preservatives used in preserved compositions may also be used as disinfecting agents in contact lens disinfecting compositions.

Various compounds are known for use as preserving agents in preserved contact lens care compositions. Examples include thimerosal, benzalkonium chloride and chlorhexidine. However, these preserving agents are known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. The degree of ocular toxicity increases when these agents are utilized as disinfecting agents. Further, a soft contact lens, a rigid gas permeable contact lens (RGP) or a hard contact lens can absorb or adsorb these compounds. This causes the contact lens to retain the irritating compound and contributes to the eye irritation and sensitivity which may result.

Other conventional methods of contact lens chemical disinfection utilize one or more active disinfecting agents in an aqueous medium, for example a chlorhexidine/thimerosal solution or a relatively mild solution of hydrogen peroxide. Some of these disinfecting solutions, such as those named above, are cytotoxic and are known to be adsorbed or absorbed onto or into a contact lens and cause the lens to elicit a cytotoxic response after disinfection. For example, contact lenses which have been soaked in a disinfecting hydrogen peroxide solution are to be treated to remove residual hydrogen peroxide, e.g., by soaking in a catalase solution, before they may be comfortably and safely worn again. If residual hydrogen peroxide remains on the lenses, then irritation to the eye may result.

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Thus, it is readily apparent that a continuing need exists for safe and efficacious compositions that can be used as contact lens disinfecting compositions and as preserved contact lens care compositions.

5 Summary of the Invention

 New disinfecting and preserved compositions and methods employing such compositions, particularly compositions and methods directed to contact lens care, have been discovered. The present compositions include
10 effective disinfectants and/or preservatives. Thus, for example, a contact lens can be effectively disinfected in a reasonable length of time. Also, contact lens care products can be effectively preserved against growth of contaminating microorganisms. Importantly, such
15 disinfecting and preserving activities are achieved, and the contact lenses disinfected or otherwise cared for using the present compositions can be safely and comfortably worn with little or no risk of eye irritation or sensitivity.

20 In one broad aspect of the invention, compositions useful for disinfecting a contact lens are provided. Such compositions comprise a liquid medium, preferably an aqueous liquid medium; a first antimicrobial component selected from the group consisting of antimicrobial
25 peptides and mixtures thereof; and a second antimicrobial component other than the first antimicrobial component. The first and second antimicrobial components together are present in an amount effective to disinfect a contact lens contacted with the composition.

30 In another broad aspect of the present invention, compositions useful for treating a contact lens are provided. These treating compositions comprise a liquid medium, preferably a liquid aqueous medium; a first antimicrobial component selected from the group consisting
35 of antimicrobial peptides and mixtures thereof; and a

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second antimicrobial component other than the first antimicrobial component. The first and second antimicrobial component together are present in an amount effective to preserve the composition.

5 An additional aspect of the present invention involves compositions useful for disinfecting a contact lens which comprise antimicrobial peptide nanotubes. The antimicrobial peptide nanotubes are present in an amount effective to disinfect a contact lens in a liquid medium
10 containing such nanotubes. In addition, these compositions preferably include a destroying component effective to destroy peptide nanotubes in an amount effective to destroy all the antimicrobial peptide nanotubes present in the compositions.

15 Methods for disinfecting contact lenses and for caring for contact lenses using the present compositions are also provided and are included within the scope of the present invention.

Detailed Description of the Invention

20 The present invention is applicable to disinfecting or otherwise caring for all types of lenses, for example, contact lenses, which are benefitted by such disinfecting or other caring. Such lenses, for example, conventional soft contact lenses, RGPs and hard contact lenses may be
25 made of any suitable material or combination of materials and may have any suitable configuration. The invention is also applicable to preserve compositions, such as contact lens care compositions and other eye care compositions, which are benefitted by being preserved.

30 One important feature of the compositions of the present invention is the inclusion of one or more antimicrobial peptides in contact lens disinfecting compositions and preserved contact lens care compositions.

35 In one embodiment, the present compositions include a sufficient amount of antimicrobial peptide nanotubes to

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effectively disinfect contact lenses contacted with the nanotube-containing compositions. In another embodiment, the present compositions include a liquid medium, a first antimicrobial component selected from the group consisting of antimicrobial peptides, preferably other than peptide nanotubes, and mixtures thereof; and a second antimicrobial component other than the first antimicrobial component, which second antimicrobial component is preferably substantially non-oxidative. The first and second antimicrobial components together are present in an amount effective to disinfect a contact lens contacted with the composition. In these compositions, the amounts of the individual first and second antimicrobial components included is preferably reduced relative to using only one of the antimicrobial components to perform the disinfecting. Thus, the reduced amounts of first and second antimicrobial components reduce the risk of eye irritation. Alternately, enhanced antimicrobial activity is obtained if disinfecting amounts of both first and second antimicrobial components are included in the compositions.

The present compositions may further include a destroying component, more preferably selected from proteolytic enzymes, for example, proteases, and mixtures thereof, effective to destroy or degrade peptides, for example, peptide nanotubes, in an amount effective to destroy or degrade all the antimicrobial peptides present in the compositions. Antimicrobial peptide nanotubes, although being very useful in the present compositions and methods, are believed to have a relatively high potential for causing irritation to ocular tissue. For this reason, if such nanotubes are employed, it is preferred that a destroying component be also used so that the contact lens is freed of the nanotubes prior to being placed into the eye, for safe and comfortable wear.

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Peptide nanotubes can be considered stacks of peptide rings. For example, cyclic peptide structures made up of a substantially even number of alternating D- and L- amino acid residues can adopt a substantially flat ring-like conformation and stack, under conditions favorable for such stacking, to produce a hollow tubular structure of sufficient length to span the thickness of the cell membranes of microorganisms. Without wishing to limit the invention to any particular theory of operation, it is believed that such hollow tubular structures are effective to penetrate the cell membranes of microorganisms to form ion-transport pores or channels therein. These pores or channels compromise the cellular and/or ionic integrity and/or stability of the microorganisms sufficiently to kill the microorganisms. Preferably, the hollow tubular structure employs hydrogen bonding to at least partially, preferably substantially totally, maintain the desired tubular structure.

The peptide nanotubes are preferably made from synthetic, rather than naturally-occurring, peptide sub-units. The peptide sub-units should preferably partition favorably into a hydrophobic phase, such as is the case with many channel-forming naturally occurring peptides, and, in addition, are preferably able to participate in extended hydrogen-bonded stacking interactions to produce channel (tubular) structures long enough to span the cell membranes of the microorganisms to be attacked.

A specific peptide sub-unit which may be employed is the cyclic peptide, cyclo[-(Trp-D-Leu)₃Gln-D-Leu-], which is composed of alternating L-tryptophan and D-leucine side-chain moieties, with the exception of one L-glutamine residue. This peptide can be made by the conventional solid phase technique (see Merrifield, J. Am. Chem. Soc. 85, 214999-2154 (1963); Barany et al, The Peptides, vol.

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2, pp. 1-284 (Gross et al, eds., Academic, New York 1979); and Rovera et al, Tetrahedron Lett, vol. 32, pp. 2639-2642 (1991), each of which is incorporated in its entirety by reference.

5 The antimicrobial peptides other than the antimicrobial peptide nanotubes useful according to the present invention include synthetic antimicrobial peptides and forms of naturally occurring antimicrobial peptides, preferably cytolytic peptides. Such peptides may be the
10 L-form, the D-form or combinations or mixtures of both forms.

 Among the antimicrobial peptides preferably employed are those selected from defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof.
15

 Particularly preferred are the cecropins, magainins and defensins. Exemplary cecropins include the peptides having the following amino acid sequences:

20 cecropin A:

 Lys Trp Lys Leu Phe Lys Lys Ile Glu Lys
 Val Gly Gln Asn Ile Arg Asp Gly Ile Ile
 Lys Ala Gly Pro Ala Val Ala Val Val Gly
25 Gln Ala Thr Gln Ile Ala Lys;

 and cecropin B:

 Lys Trp Lys Val Phe Lys Lys Ile Glu Lys
30 Met Gly Arg Asn Ile Arg Asn Gly Ile Val
 Lys Ala Gly Pro Ala Ile Ala Val Leu Gly
 Glu Ala Lys Ala Leu Gly.

Cecropin D can also be employed.

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Other defensins and defensin analogs, such as those described in Selsted et al, J. Clin. Invest. 76, 1436-1439 (October 1985), and Kagan et al, Proc. Natl. Acad. Sci. USA 87, 210-214 (January 1990), each of which is
5 incorporated in its entirety herein by reference, are also useful in the present invention.

The defensins are nonhelical pore formers, unlike the magainins and cecropins. However, analogues which mimic essential aspects of the native peptide conformation
10 (assumed to be antiparallel beta-sheet) are preferred. Therefore, proper pairing and disulfide bonding of cysteine residues is desirable to ensure that the peptide is folded into the appropriate channel forming conformation.

15 Tachyplesins, such as tachyplesin I and II, and polyphemusins, such as polyphemusin I and II, are defensin-like peptides. See, e.g., Ohta et al, Antimicrobial Agents and Chemotherapy 36 (No. 7), 1460-1465 (July 1992), which is incorporated in its entirety
20 herein by reference. These peptides and antimicrobially active derivatives thereof are also contemplated as being useful in the present invention.

Other peptides, such as hybrids (peptides comprised of sequences from several antimicrobial classes), e.g.,
25 cecropin-melittin hybrids, and peptide analogs in which one or more of the L-amino acids are replaced with other L-amino acids, can also be used with advantage provided that they retain sufficient antimicrobial activity.

Exemplary hybrid peptides include cecropin A-(1-8)-
30 melittin-(1-18)-NH₂:

Lys Trp Lys Leu Phe Lys Lys Ile Gly Ile
Gly Ala Val Leu Lys Val Leu Thr Thr Gly
Leu Pro Ala Leu Ile Ser-NH₂;

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and cecropin A-(1-3)-melittin-(1-13)-NH₂:

Lys Trp Lys Gly Ile Gly Ala Val Leu Lys
Val Leu Thr Thr Gly Leu-NH₂.

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Melittin itself, however, is unsuitable for use due to its high toxicity.

The antimicrobial agents must be compatible with the contact lens being disinfected. The antimicrobial peptides should also be non-toxic to humans.

Antimicrobial agents useful according to the invention can be prepared using techniques well known to those skilled in the art. Antimicrobial peptides can be prepared by the solid-phase synthesis technique noted previously. Exemplary processes for preparing antimicrobial peptides are given in Wade et al, Proc. Natl. Acad. Sci. USA 87, 4761-4765 (June 1990), and Bessale et al, FEBS Letters 274, no. 1,2, 151-155 (November 1990), each of which is incorporated herein in its entirety by reference.

The second or other antimicrobial component employed in the present invention is other than the first antimicrobial component and preferably is other than antimicrobial peptide nanotubes. This second antimicrobial component is more preferably selected from synthetic polymeric antimicrobial components and mixtures thereof.

As used herein, substantially non-oxidative antimicrobial components include effectively non-oxidative organic chemicals, for example, synthetic polymers, which derive their antimicrobial activity through a chemical or physiochemical interaction with the microbes or microorganisms. Suitable non-oxidative antimicrobial components include, but are not limited to, quaternary

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ammonium salts used in ophthalmic applications such as poly[dimethylimino-2-butene-1,4-diyl] chloride, alpha- [4-tris(2-hydroxyethyl) ammonium]-dichloride (chemical registry number 75345-27-6, available under the trademark polyquarternium 1[®] from ONYX Corporation), benzalkonium halides, and biguanides such as salts of alexidine, alexidine-free base, salts of chlorhexidine, hexamethylene biguanides and their polymers, antimicrobial polypeptides, and the like and mixtures thereof. A particularly useful substantially non-oxidative antimicrobial component is selected from polyhexamethylene biguanide (PHMB), N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium-1, hexetidine, bronopol, alexidine, ophthalmically acceptable salts thereof and mixtures thereof.

The salts of alexidine and chlorhexidine can be either organic or inorganic and are typically disinfecting gluconates, nitrates, acetates, phosphates, sulphates, halides and the like. Generally, the hexamethylene biguanide polymers, also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in Ogunbiyi et al U.S. Patent No. 4,758,595, the disclosure of which is incorporated in its entirety herein by reference.

The substantially non-oxidative antimicrobial components useful in the present invention are preferably present in the liquid aqueous medium in concentrations in the range of about 0.000005% or about 0.00001% to about 2% (w/v).

More preferably the substantially non-oxidative antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration such that the user can remove the disinfected lens from the liquid aqueous medium/matrix

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No. 3,910,296, which disclosures are incorporated herein by reference.

In one embodiment, a cleaning enzyme component, for example, a proteolytic enzyme component, can be used to remove debris from the contact lens and, in addition, can be used as a destroying component to destroy the antimicrobial peptide nanotubes and/or antimicrobial peptides being employed, when such destruction is desired.

Preferred proteolytic enzymes are those which are substantially free of sulfhydryl groups or disulfide bonds. Metallo-proteases, those enzymes which contain a divalent metal ion such as calcium, magnesium or zinc bound to the protein, may also be used.

A more preferred group of proteolytic enzymes are the serine proteases, particularly those derived from Bacillus and Streptomyces bacteria and Aspergillus molds. Within this grouping, the still more preferred enzymes are the derived alkaline proteases generically called subtilisin enzymes. Reference is made to Keay, L., Moser, P.W. and Wildi, B.S., "Proteases of the Genus Bacillus". II. Alkaline Proteases, "Biotechnology and Bioengineering", Vol. XII, pp 213-249 (1970, March) and Keay, L. and Moser, P.W., "Differentiation of Alkaline Proteases form Bacillus Species" Biochemical and Biophysical Research Comm., Vol 34, No. 5, pp 500-504, (1969).

The subtilisin enzymes are broken down onto two sub-classes, subtilisin A and subtilisin B. In the subtilisin A grouping are enzymes derived from such species as B. subtilis, B. licheniformis and B. pumilis. Organisms in this sub-class produce little or no neutral protease or amylase. The subtilisin B sub-class is made up of enzymes from such organisms as B. subtilis, B. subtilis var. amylosaccharificus, B. amyloliquefaciens and B. subtilis NRRL B3411. These organisms produce neutral proteases and amylases on a level about comparable to their alkaline

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protease production. One or more enzymes from the subtilisin A sub-class are particularly useful.

In addition other preferred enzymes are, for example, pancreatin, trypsin, collagenase, keratinase, carboxylase, aminopeptidase, elastase, and aspergillo-peptidase A and B, pronase E (from S. griseus) and dispase (from B. polymyxa).

An effective amount of proteolytic enzyme is preferably used in the practice of this invention. Such amount will be that amount which effects removal in a reasonable time (for example about 4 hours to overnight) of substantially all protein-based or proteinaceous deposits from a contact lens due to normal wear. This standard is stated with reference to contact lens wearers with a history of normal pattern of protein accretion, not the very small group who may at one time or another have a significantly increased rate of protein deposit such that cleaning is recommended every day, or every two or three days.

The amount of enzyme required to make an effective cleaner will depend on several factors, including the inherent activity of the enzyme, and the excipient it contains.

As a basic yardstick, the working solution should contain sufficient enzyme to provide about 0.001 to about 3 Anson units of activity, preferably about 0.01 to about 1 Anson units, per single lens treatment. Higher or lower amounts may be used.

Enzyme activity is pH dependent. Thus, for any given enzyme, there is a particular pH range in which that enzyme will function best. The determination of such range can readily be done by known techniques.

One or more additional components can be included in the present compositions based on the particular application for which the compositions are formulated.

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Thus, the present compositions can be formulated as disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions, soaking compositions and the like. Also, the present compositions can be formulated to be useful in performing two or more contact lens care operations. For example, a disinfecting/cleaning composition, or a cleaning/conditioning composition or even an all purpose lens care composition can be formulated and such multi-functional compositions are included within the scope of the present invention.

The additional component or components included in the present compositions are chosen to impart or provide at least one beneficial or desired property to the compositions. Such additional components may be selected from components which are conventionally used in one or more contact lens care compositions. Examples of such additional components include buffering agents, cleaning agents, wetting agents, sequestering agents, viscosity builders, tonicity agents, nutrient agents, contact lens conditioning agents, antioxidants, pH adjustors, and the like. These additional components are each included in the present compositions in an amount effective to impart or provide the beneficial or desired property to the compositions. For example, such additional components may be included in the present compositions in amounts similar to the amounts of such components used in other, e.g., conventional, contact lens care products.

Useful buffering agents include, but not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids and bases may be used to adjust the pH of the present compositions as needed.

Useful wetting agents include, but are not limited to, polyvinyl alcohol, polyoxamers, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose and mixtures thereof.

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EXAMPLE 1

The following composition is prepared by blending together the ingredients.

	<u>Ingredient</u>	<u>% w/v</u>
5	Cecropin	5 ppm
	PHMB (polyhexamethylene biguanide)	0.5 ppm
	Edetate disodium, USP	0.05
10	Sodium chloride, USP	0.37
	Hydrochloric acid	adjust to pH 7.5
	Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a soft contact lens disinfecting composition.

EXAMPLE 2

The following composition is prepared by blending together the ingredients.

	<u>Ingredient</u>	<u>% w/v</u>
20	Cecropin	5 ppm
	PHMB (polyhexamethylene biguanide)	0.5 ppm
25	Hydroxyethyl cellulose, NF	0.65
	Sodium chloride, USP	0.67
	Boric acid, NF	0.39
	Sodium borate decahydrate, NF	0.20
	Edetate disodium, USP	0.127
30	Water, U.S.P.	Q.S. to 100%

This composition is formulated as and is effective as a soft contact lens disinfecting and conditioning composition.

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EXAMPLE 3

The following composition is prepared by blending together the ingredients.

	<u>Ingredient</u>	<u>% w/v</u>
5	Cecropin	1 ppm
	PHMB (polyhexamethylene biguanide)	0.1 ppm
	Hydroxyethyl cellulose, NF	0.65
10	Sodium chloride, USP	0.67
	Boric acid, NF	0.39
	Sodium borate decahydrate, NF	0.20
	Edetate disodium, USP	0.127
	Water, U.S.P.	Q.S. to 100%

15

This composition is formulated as and is effective as a preserved soft contact lens soaking/conditioning composition

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EXAMPLE 4

The following composition is prepared by blending together the ingredients.

	<u>Ingredient</u>	<u>% w/v</u>
	Defensin	5 ppm
25	PHMB (polyhexamethylene biguanide)	0.5 ppm
	Boric acid	0.39
	Edetate disodium	0.1
30	Sodium chloride	0.40
	Sodium borate decahydrate, NF	0.20
	Pluronic F-127	0.10
	Water, U.S.P.	Q.S. to 100%

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This composition is formulated as and is effective as a soft contact lens disinfecting/cleaning composition.

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EXAMPLE 5

The following composition is prepared by blending together the ingredients.

	<u>Ingredient</u>	<u>% w/v</u>
5	Defensin	1 ppm
	PHMB (polyhexamethylene biguanide)	0.1 ppm
	Boric acid	0.39
10	Edetate disodium	0.1
	Sodium chloride	0.40
	Sodium borate decahydrate, NF	0.20
	Pluronic F-127	0.10
	Water, U.S.P.	Q.S. to 100%

15

This composition is formulated as and is effective as a preserved soft contact lens cleaning composition.

EXAMPLE 6

20 The following composition is prepared by blending together the various ingredients.

	<u>Ingredient</u>	
	cyclo [-(Trp-D-Leu) ₃ -Gln-D-Leu]	25 ppm
	Sodium chloride	137 mM*
25	Potassium chloride	2.6 mM*
	Sodium hydrogen phosphate	6.4 mM*
	Potassium dihydrogen phosphate	1.4 mM*
	pH	6.5
	Water, U.S.P.	Q.S. to 100%

30

*Concentration expressed as millimolar.

This composition is formulated as and is effective as a contact lens disinfecting composition. The peptide, cyclo [-(Trp-D-Leu)₃-Gln-D-Leu], forms, for example, self

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that it can be variously practiced within the scope of the following claims.

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WHAT IS CLAIMED IS:

1. A method for disinfecting a contact lens comprising:

5 contacting a contact lens with a liquid medium including antimicrobial peptide nanotubes in an effective contact lens disinfecting amount, thereby disinfecting said contact lens.

2. The method of claim 1 wherein said antimicrobial peptide nanotubes are synthetic, and which further comprises, after said contacting, placing said contact lens in an environment substantially free of said antimicrobial peptide nanotubes prior to placing said
5 contact lens in an eye.

3. The method of claim 1 which further comprises, after said contacting, destroying substantially all of said antimicrobial peptide nanotubes in said liquid medium.

4. The method of claim 3 wherein said destroying step includes placing an enzyme component in said liquid medium in an amount effective to destroy substantially all of said antimicrobial peptide nanotubes in said liquid
5 medium.

5. The method of claim 4 wherein said enzyme component is effective in removing protein-based deposit material from said contact lens in said liquid medium.

6. A combination comprising:
 an aqueous liquid medium;
 a contact lens in contact with said aqueous
liquid medium; and

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5 antimicrobial peptide nanotubes present in said aqueous liquid medium in an amount effective to disinfect said contact lens.

7. A composition useful in disinfecting a contact lens comprising:

5 antimicrobial peptide nanotubes in an amount effective to disinfect a contact lens in a liquid medium containing said antimicrobial peptide nanotubes; and

a destroying component effective to destroy peptide nanotubes in an amount effective to destroy all of said antimicrobial peptide nanotubes.

8. The composition of claim 7 wherein said antimicrobial peptide nanotubes are synthetic and which further comprises a barrier component in an amount effective to prevent the release of said destroying component in a liquid medium for a period of time sufficient to allow the disinfection of a contact lens placed into a liquid medium containing said antimicrobial peptide nanotubes at the same time said destroying component and said barrier component are placed into the liquid medium.

9. The composition of claim 7 which further comprises an aqueous liquid medium and includes an effective amount of an ophthalmically acceptable pH buffer component.

10. A method of disinfecting a contact lens comprising:

5 contacting a contact lens with a liquid medium including a combination of a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof, and a second antimicrobial

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component other than said first antimicrobial component, said combination being present in an effective contact lens disinfecting amount, thereby disinfecting said contact lens.

11. The method of claim 10 wherein said first antimicrobial component is selected from the group consisting of antimicrobial peptides other than synthetic antimicrobial peptide nanotubes, and said second
5 antimicrobial component is substantially non-oxidative.

12. The method of claim 11 which further comprises, after said contacting, placing said contact lens directly from said liquid medium into a mammalian eye.

13. The method of claim 10 wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof and
5 said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

14. A method for treating a contact lens comprising:
contacting a contact lens with a liquid medium
including a combination of a first antimicrobial component
selected from antimicrobial peptides and mixtures thereof,
5 and a second antimicrobial component other than said first antimicrobial component, said combination being present in an amount effective to preserve said liquid medium.

15. The method of claim 14 wherein said second antimicrobial component is substantially non-oxidative, and said method further comprises, after said contacting,

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placing said contact lens directly from said liquid medium into a mammalian eye.

16. The method of claim 14 wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof and said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

17. A composition useful in disinfecting a contact lens comprising:

a liquid medium;

a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof; and

a second antimicrobial component other than said first antimicrobial component, said first antimicrobial component and said second antimicrobial component together being present in an amount effective to disinfect a contact lens contacted with said composition.

18. The composition of claim 17 wherein said first antimicrobial component is selected from the group consisting of antimicrobial peptides other than synthetic antimicrobial peptide nanotubes, and said second antimicrobial component is substantially non-oxidative.

19. The composition of claim 17 wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof, and

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said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

20. A composition useful for treating a contact lens comprising:

a liquid medium;

5 a first antimicrobial component selected from the group consisting of antimicrobial peptides and mixtures thereof; and

10 a second antimicrobial component other than said first antimicrobial component, said first antimicrobial component and said second antimicrobial component together being present in an amount effective to preserve said composition.

21. The composition of claim 20 which is ophthalmically acceptable, and wherein said first antimicrobial component is selected from the group consisting of defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins, peptides related to magainins and mixtures thereof, and said second antimicrobial component is selected from synthetic polymeric antimicrobial components and mixtures thereof.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US96/01728 (22) International Filing Date: 8 February 1996 (08.02.96) (30) Priority Data: 08/390.006 17 February 1995 (17.02.95) US (71) Applicant: ALLERGAN, INC. [US/US]: 8301 Mars Drive, Waco, TX 76712 (US). (72) Inventors: HUTH, Stanley, W.; 1975 Port Laurent Place, Newport Beach, CA 92660 (US). CURRIE, James, P.; 28746 Vista Santiago Drive, Trabuco Canyon, CA 92679 (US). BAKER, John, C.; 3 Yankee, Irvine, CA 92720 (US). (74) Agents: KING, Timothy, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limits for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 10 October 1996 (10.10.96) RECEIVED OCT 23 1996 LEGAL / PATENTS
(54) Title: OPHTHALMIC COMPOSITIONS INCLUDING PEPTIDES AND PEPTIDE DERIVATIVES AND METHODS FOR USING SAME (57) Abstract Ophthalmic compositions and methods for preserving and using such compositions are disclosed. In one embodiment, such compositions include a liquid medium, a first antimicrobial component selected from antimicrobial peptides and mixtures thereof, and a second antimicrobial component, other than the first antimicrobial component, which is preferably substantially non-oxidative. Compositions which include a liquid medium and antimicrobial peptide nanotubes effective to disinfect a contact lens present in the liquid medium containing the nanotubes are also disclosed. Preserved compositions useful for caring for contact lenses are included within the scope of the present invention.		

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/01728

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61L2/18 A01N47/44 A01N37/46 //(A01N47/44,37:46)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61L C07K A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO,A,96 06532 (NOVO NORDISK) 7 March 1996 see claims 1,6,17,22	1,2,6
X	US,A,4 659 692 (LEHRER R.I.) 21 April 1987 see column 6, line 13; claims 1,13	1,2,6
A	WO,A,94 21672 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 29 September 1994 see claim 1	7
A	US,A,5 242 902 (MURPHY C.J.) 7 September 1993 see claims 1,6,10	6
A	WO,A,91 07192 (SCHERING) 30 May 1991 see claim 6	13,16, 19,21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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9 August 1996

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In: section on patent family members

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